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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,187	03/18/2004	Thomas Christoph	029310.53299US	5120

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CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER

FRAZIER, BARBARA S

ART UNIT	PAPER NUMBER
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1611

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/803,187	Applicant(s) CHRISTOPH, THOMAS	
	Examiner BARBARA FRAZIER	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 November 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37-41, 48-57 and 73 is/are pending in the application.
- 4a) Of the above claim(s) 38, 40, 41, 52 and 53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37, 39, 48-51, 54-57 and 73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. Claims 37-41, 48-57, and 73 are pending in this application.
2. Cancellation of claims 44-47 and 58-72 is acknowledged. Claims 1-36, 42, and 43 already stand canceled.
3. Claims 38, 40, 41, 52, and 53 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 9/27/07.
4. Claims 37, 39, 48-51, 54-57, and 73 are examined.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. **Claims 37, 39, 48-51, 54-57, and 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595 and cited by Applicant), in view of Buschmann (US Patent 6248,737) and Andersson et al**

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("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947 and cited by Applicant).

The claimed invention is drawn to a composition comprising an admixture of an analgesic and an anti-muscarinic agent (see claim 37); Applicants have elected (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride as the analgesic (see claims 37, 39, 48-51, and 54-57). The antimuscarinic agent is selected from the group consisting of atropine, oxybutinin, propiverine, propantheline, emepronium, trospium, tolterodine, darifenacin and α , α -diphenylacetic acid 4-(N-methylpiperidyl) ester, duloxetine, imipramine and desmopressin (claim 37).

Chutka et al teach that both anticholinergic drugs (i.e., antimuscarinic agents) and opioids can decrease the contraction of the detrusor by impairing the contractility of the detrusor and potentially lead to urinary retention (see, e.g., page 593, third paragraph, and Table 1).

Chutka et al do not specifically teach the combination of an analgesic such as (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent such as one of those recited in claim 37.

Buschmann '737 teach 1-phenyl-3-dimethylaminopropane compounds with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids, and which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with the opioid tramadol in some cases, and which has a significantly enhanced analgesic effect compared with that of tramadol (col. 1, lines 52-65). Buschmann '737 teaches a method of making and

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separating the (+) enantiomer of (2R, 3R)- 1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol (Example 1, column 6, line 23 to column 7, line 61). Buschmann '737 teaches that the (+) enantiomer of (2R, 3R)-1-dimethylamino- 3-(3-methylphenyl)-2-methylpentan-3-ol is a superior analgesic compared to the racemic mixture or (-) enantiomer (column 23, Table).

Andersson et al teach pharmaceutical substances that are known to treat urinary incontinence (Title) and include anti-muscarinic (i.e., anticholinergic) agents such as atropine, propantheline, emepronium, trospium, tolterodine, darifenacin, oxybutynin and propiverine (pages 924 and 925, table 2). Andersson et al teach that one such anti-muscarinic agent, oxybutynin, has well documented efficacy in the treatment of detrusor hyperactivity, is available in various forms, and is probably the drug of first choice in patients with detrusor hyperactivity (page 930, column 2, third and fifth full paragraphs).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to combine an admixture of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation success, for the following reasons: First, one skilled in the art would be motivated to combine an opioid and an anticholinergic agent, since both are known to impair detrusor contraction, as taught by Chutka et al. It is prima facie obvious to combine two compositions, each of which is taught by the prior art, to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06. Second, one skilled in the art would be

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motivated to substitute (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride for an opioid, since the aminopropane compound has an enhanced analgesic effect compared to an opioid (and therefore would be reasonably expected to have the same or improved efficacy in relaxing bladder muscles as well) but without the negative side effects, as taught by Buschmann '737. Third, one skilled in the art would be motivated to select one of the antimuscarinic agents listed in claim 37 because a number of said compounds are known to be effective as antimuscarinic agents, and one of them (oxybutinin) is even known as the "drug of choice", as taught by Andersson et al.

Regarding claim 73, Buschmann '737 teaches that the analgesics are administered with pharmaceutically suitable auxiliary substances (see col. 5, lines 48-67).

Response to Arguments and Data in Specification

7. Applicant's arguments filed 11/03/09 have been fully considered but they are not persuasive.

Applicants argue that the presently claimed composition of matter is nonobvious over the combination of cited references because the presently claimed composition of matter exhibits an unexpected synergistic effect in the treatment of urinary incontinence, citing Example 1 of the specification. Applicants argue that the test data demonstrating the unexpected synergistic effect is commensurate with the scope of the claims.

Applicants assert that the tested (+)-(2R, 3R)-dimethylamino-3-(3-methoxy-phenyl)-2-

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methyl-pentan-3-ol hydrochloride enantiomer is representative of the claimed 1-phenyl-3-dimethylamino-propane compounds of formula I. Applicants also argue that there is no reason to believe that the synergistic effect shown in Example 1 is limited to the particular dosages tested in Example 1, asserting that synergistic effect is not typically dose dependent, and that the Office Action does not provide any reason that the synergistic effect would be limited to the particular dosages tested.

This argument is not persuasive. Applicant's data in the specification has been fully considered, but is not deemed persuasive for overcoming the rejection. First, the Examiner disagrees that the tested (+)-(2R, 3R)-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride enantiomer is representative of the claimed 1-phenyl-3-dimethylamino-propane compounds of formula I. While Buschmann '737 generally teaches that 1-phenyl-3-dimethylaminopropane compounds exhibit an analgesic effect, Buschmann '737 specifically teaches that (+) enantiomer of (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol is a superior analgesic compared to the racemic mixture or (-) enantiomer (column 23, Table), which are also encompassed by the formula I compounds of the claimed invention. Since Buschmann '737 teach that the enantiomer exhibits a superior effect compared to the racemic mixture or (-) enantiomer, the probative value of the combination of the (+) enantiomer and oxybutynin cannot reasonably be extended to other 1-phenyl-3-dimethylaminopropane compounds of formula I in the claimed invention. Second, the Examiner disagrees with Applicant's assertion that synergistic effect is not typically dose dependent. In response to Applicant's argument, the Examiner cites U.S. Patent 4,442,084 as an example of

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dose-dependent synergism in analgesic compositions (see columns 6 and 7). One skilled in the art would further reasonably expect synergism to be dose dependent because, if the amount of one of the components is very small, it would not be expected to contribute to the efficacy of the combination. Conversely, if the amount of one of the components is very large, one skilled in the art would not expect the addition of another component to potentiate the effects of the component present in large amounts.

Therefore, one skilled in the art would reasonably expect there to be a range of dosages at which synergism might occur. Since Applicant has provided data for only a single dosage of each component in the composition, one of ordinary skill in the art would not be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. See MPEP 716.02(d).

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Ashwin Mehta/
Primary Examiner, Technology Center 1600